REMARKS

The undersigned submits herewith a newly executed Associate Power of Attorney and a change of Correspondence of Address Form.

Claims 1-68 have been canceled without prejudice to pursue the subject matter of the canceled claims in one or more related applications. New claims 69-104 have been added to more particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. The claims are fully supported by the instant specification. In particular support for the claims is provided *inter alia* in the specification at pp. 6-8, 17, 19-20, 28, 29-30. Accordingly no new matter has been added. The Examiner contends that the information disclosure statement filed October 24, 2002 fails to comply with 37 C.F.R. § 1.98(a)(2). In order to be fully responsive, Applicants will be providing a courtesy copy of the Information Disclosure Statement as filed under separate transmittal.

After entry of this amendment claims 69-104 will be pending in the application.

1. THE CLAIMED INVENTION

The claimed invention relates to delivery of substances, including therapeutic and diagnostic substances, to the intradermal compartment of human skin to achieve systemic distribution of that substance in the human body such that the dosage of the substance for achieving the desired biological effect is reduced compared to when the substance is delivered to the subcutaneous compartment. By way of background, human skin is composed of two major tissue layers, an outer epidermis, and an underlying dermis. The epidermis of human skin is made up of five layers (the outermost impermeable barrier is called the stratum corneum) and has a total thickness of about 75 μm to 150 μm. The dermis lies beneath the epidermis, beginning at a depth of about 60 μm - 120 μm below the skin surface, and is approximately 1-2 mm thick. The dermis contains two layers — the uppermost portion contains a bed of capillary and lymphatic vessels. The lower layer is relatively avascular, composed of dense connective tissue. Beneath the epidermis and dermis is the subcutaneous tissue, composed of connective tissue and fatty tissue. Muscle tissue lies beneath the subcutaneous tissue.

Systemic distribution of drugs is best achieved by direct injection into a vein, *i.e.*, intravenous (IV) administration. However, IV injections are often impractical, requiring

trained health care specialists for administration. As a result, intramuscular (IM) and subcutaneous (SC) injections (*i.e.*, injections *below* the skin) are the most commonly used routes of administration, even though these modes of administration result in a different pharmacokinetic profile and lower bioavailability (*i.e.*, lower plasma concentration of drug).

The present invention relates to delivering substances to the intradermal compartment of human skin to achieve systemic distribution of the substance in the human body. The space in the intradermal compartment that is targeted in accordance with the invention is close to the capillary bed, allowing for absorption and systemic distribution of the substance, but is above the peripheral nerve net, thereby eliminating or reducing injection pain. The inventors have unexpectedly found that delivery of substances, drugs, for example, to the intradermal compartment results in systemic distribution with a much improved bioavailability; *e.g.*, a higher plasma level of circulating drug is achieved in a shorter time period (*see* instant specification at Examples 1, Figure 1). The direct benefit is that intradermal administration with enhanced bioavailability allows equivalent biological effect while using less active agent. This results in overall reduced dosing of the drug providing therapeutic (*e.g.*, reduced side effects) as well as economic benefits over conventional modes of delivery including subcutaneous delivery (See Example VI, Example VIII).

2. THE REJECTION UNDER 35 U.S.C. 112, 2nd PARAGRAPH SHOULD BE WITHDRAWN

Claims 21 and 46 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as their invention. Specifically, the Examiner contends that the recitation "microneedle has an outlet of from 0 to 1 mm" is indefinite as one cannot ascertain of the dimension is referring to the diameter, height or length of the outlet. Applicants respectfully disagree and contend that the this parameter has been defined in the specification, see for example p. 17. However, in view of the present claim amendments, the Examiner's rejection is moot and should be withdrawn.

3. CLAIM OBJECTIONS

The Examiner has objected to claims 17 and 39. However, in view of the claim amendments the Examiner's objection is moot and should be withdrawn.

4. THE CLAIMED INVENTION IS NOT ANTICIPATED BY U.S. Patent No. 5,527,288 ("Gross-I")

Claims 1-3, 9, 10-22, 31-40, 44-47, 51, 55-58, and 62-63 are rejected under 35 U.S.C. §102(b) as anticipated by Gross *et al.* U.S. Patent No. 5,527,288 ("Gross-I"). The Examiner contends that Gross-I discloses an intradermal drug delivery device that includes administering a substance using small gauge needles to deliver a substance into the intradermal compartment within skin. However, as Applicants discuss below, the amended claims are not anticipated by Gross-I, and the rejection should be withdrawn.

Gross-I proposes methods and devices that non-selectively administer drugs below the epidermis. Gross-I does not describe delivering or targeting drugs into the intradermal compartment to achieve the systemic distribution and dose sparing effects claimed by Applicants. Thus, the claims are not anticipated by Gross-I, and the rejection should be withdrawn.

The claimed invention relates to delivering a substance (*e.g.*, a drug or a diagnostic substance) into the intradermal compartment of a human subject's skin so that the substance is systemically distributed and the dosage of the substance for achieving a biologic effect (*e.g.*, a therapeutic or diagnostic effect) is reduced compared to when the same substance is delivered by other routes, *e.g.*, SC delivery. By delivering a substance to the intradermal space in accordance with the instant invention the substance is systemically distributed through the vasculature resulting in higher bioavailabilities of the substance. The enhanced bioavailabilities of substances delivered in accordance with the methods of the invention allows equivalent biological effects while using a reduced dose of the substance.

The devices described in Gross-I do not have the correct needle length and configuration to deliver a drug to the intradermal compartment of human skin, and achieve systemic distribution of the drug in the human subject thus resulting in dose sparing, which is the subject matter of the claimed invention. In particular, the range of lengths described by Gross-I for its single needle delivery devices (*i.e.*, 0.3 mm to 3 mm; *see, e.g.*, Gross-I at col. 2, *ll* 16-20) would result in outlet depths that are too shallow at the lower end of the range, or too deep at the higher end of the range to target the intradermal compartment of human skin; and, instead will result in delivery of the drug to the human epidermis or subcutaneous tissue.

By contrast, Applicants teach administration at a depth of at least about 0.3 mm, more preferably, at least about 0.4 mm, and most preferably at least about 0.5 mm up to a depth of no more than 2.5 mm, more preferably no more than about 2.0 mm and most preferably no more that 1.7 mm (See specification at pp. 6-7). According to Applicants' teaching,

placement and deposition of the substance at greater depths or into the lower portion of the reticular dermis would result in the substance to be slowly absorbed in the less vascular reticular dermis or into the SC region leading to reduced absorption of the substance systemically.

The Examiner erroneously contends that Gross-I discloses an outlet at a depth of about 0.3 to 1.0 mm. Moreover, a careful reading of the cited sections and the reference as a whole indicates that no disclosure relating to the relative needle length and outlet depth can be found in Gross-I. It appears that the Examiner, perhaps unwittingly, has attributed disparate teachings from the Applicants' specification into the prior art. This is improper.

Gross-I is devoid of any teaching relating to the configuration of the needle required to prevent leakage of the drug substance outside the intradermal space. It is the Applicants' disclosure, not Gross, which teaches the importance of not only the length of the needle, but the relative exposed height of the needle outlet (*e.g.*, the bevel) that could be used to successfully target the intradermal compartment. (*See*, specification at pp. 13-14, 16, 17). Unless the skin seals around the needle, the drug substance will effuse out of the skin due to backpressure exerted by the skin itself, or the pressure built up from the accumulating fluid. The Applicants' specification sets forth principles and parameters relating to length of the needle and configuration of its outlet to prevent unwanted leakage. The Applicants' teachings also address mechanisms that can be used to provide adequate pressure so that the drug is efficiently and consistently delivered to the intradermal compartment of human skin where it is readily absorbed and systemically distributed. In particular, the specification describes the use of microneedles that have *both* a length sufficient to penetrate the intradermal space *and* an *outlet depth within the penetration space* to allow the skin to seal around the needle to prevent effusion of the substance onto the surface of the skin due to backpressure *(See*, specification at *See*, specification at pp. 13-14, 16, 17). Gross-I neither appreciates nor addresses the significance of these parameters for practicing the claimed method.

Gross-I also fails to appreciate the complications associated with true intradermal delivery in human subjects, such as those resulting from backpressure exerted by the skin itself and the pressure built up from accumulating fluid. This failure may be attributable to Gross-I's use of an inappropriate animal model (*e.g.*, a rabbit as demonstrated in Example 1 of Gross-I at col.10, *l.* 60 to col. 11, *l.* 7) in which the skin thickness does not provide the correct approximation to that of human skin. (*See*, Corbo *et al.*, 1989, *Pharmaceutical Research*, 6(9): 753-8, Exhibit A). The prototype model for human skin, as acknowledged by

those skilled in the art, is pig since the thickness of the pig's various skin compartments most closely approximates human skin. (*See,* Bronaugh *et al.*, 1982, *Toxicology & Applied Pharmacology*, 62:481-8, Exhibit A). The pig model is precisely the one used by Applicants (*See* specification at Example I, II, IV, V).

Gross-I also fails to appreciate that delivering the substance to the intradermal compartment of a subject's skin leads to enhanced bioavailability of the substance and thus reduced dosing of the substance as compared to when the substance is deposited in the SC compartment. Gross-I simply provides no comparative analysis with alternative routes of delivery to its alleged "intradermal" delivery. Applicants specifically set forth Examples where the dose sparing of the intradermal delivery of therapeutics substances is compared to SC delivery (See Examples VII and VIII).

Gross-I does not describe, measure or evaluate the systemic distribution or pharmacokinetic profile of any drug, and does not appreciate the dose sparing effects resulting therefrom. Therefore, Gross-I does not expressly anticipate the claims. Moreover, inherent anticipation cannot be found because the devices and methods described in Gross-I do not achieve the claimed systemic distribution, pharmacokinetic profiles and dose sparing effects of a drug targeted to the intradermal space. In fact, the data reported by Gross-I demonstrate that targeted delivery to the intradermal compartment is not achieved using the Gross-I devices (Example I).

For example, if Gross-I had actually delivered drug to the intradermal compartment, the entire dose of insulin administered in Example 1, *i.e.*, 20 I.U. of insulin, would have been distributed systemically in the animal's bloodstream.[1] As a result, the 20 I.U. of insulin would have been bioavailable, and the animals treated in Example 1 would have died due to hypoglycemic shock.[2] *See*, Exhibit B, Marian *et al.*, 2001, *Acta Biologica Hungarica* 52(1):

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[1] According to Example 1, an insulin solution of 100 I.U./mL was infused to the rabbit at a rate of 0.1 mL/hour for two hours. Therefore, a total volume of 0.2 mL was administered (0.1 mL/hr. x 2hr. = 0.2 mL). 0.2 mL of an insulin solution of 100 I.U./mL translates into a total administration of 20 I.U. of insulin (0.2 mL x 100 I.U./mL = 20 I.U.)

[2] Had the entire bioavailable dose been delivered by any means described in the Gross patent, in the absence of intervention, the animals would have died due to hypoglycemic shock. Traditionally, 15-20 I.U. insulin has been used to induce hypoglycemia in experimental rabbits; without anesthesia or simultaneous administration of carbohydrates, the animals would fall into hypoglycemic coma and perish in the attendant convulsion. *See, e.g.*, Exhibit D, Sveinsson, 1939, *Investigations on the Influence of Insulin and Adrenalin in Rabbits with Alimentary Fatty Liver: The Effect of Insulin and Adrenalin on the Content of*

35-45 and Sveinsson, 1939, *Investigations on the Influence of Insulin and Adrenalin in Rabbits with Alimentary Fatty Liver: The Effect of Insulin and Adrenalin on the Content of Fat and Glycogen in Liver and Muscles and on the Content of Fat and Sugar in Blood* (pp. 66-86), Oslo, Norway. Instead, the animals lived long enough for Gross to monitor blood glucose levels, which increased at the end of infusion (Gross-I Fig. 12).[3]

A number of factors may explain the failure of Gross-I to deliver the full dose of insulin systemically -- but the "take-home" lesson is that targeted delivery to the intradermal space was not achieved! For example, the drug may have leaked out to the surface of the skin due to defective sealing; alternatively, inappropriate outlet depths may have resulted in subcutaneous or intramuscular delivery and lower bioavailability of drug. In other words, the parameters of needle lengths provided by Gross-I result in administration of the drug either at a depth too shallow to overcome the pressure exerted by the skin to achieve intradermal delivery of clinically useful amounts of the drug, or at a depth too deep so that subcutaneous drug delivery is achieved, rather than intradermal delivery.

In view of the foregoing, Gross-I does *not* teach *delivering* drug into the *intradermal compartment* of a subject's skin to achieve dose sparing benefits as claimed in the instant application, and as such Gross does not anticipate the claimed invention. Anticipation can only be established by a single prior art reference that describes *each and every element* of the claimed invention. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q. 2d 1896 (Fed. Cir. 1991). Nothing in Gross-I describes or even suggests *delivering* a substance into the intradermal compartment of a subject's skin for systemic distribution of the substance having the dose sparing effects claimed.

Moreover, Gross-I does not inherently anticipate the claimed invention. In order for a prior art reference to amount to an inherent anticipation of a claim, all the elements of the claim must *necessarily*, *inevitably* and *always* result from the prior art disclosure; mere possibilities or probabilities are not sufficient. *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981) (citing *Hansgirg v. Kemmer*, 102 F.2d 212, 214, 40 U.S.P.Q. 665, 667 (C.C.P.A. 1939). Furthermore, an accidental or unwitting duplication of

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Fat and Glycogen in Liver and Muscles and on the Content of Fat and Sugar in Blood (pp. 66-86), Oslo, Norway; Marian *et al.*, 2001, *Acta Biologica Hungarica* 52(1): 35-45).

[3] Again, we emphasize that Gross did not measure the pharmacokinetic profile or report any insulin levels in the animal's bloodstream -- instead, an *indirect* pharmacodynamic measurement of blood glucose was reported.

an invention may not constitute an anticipation. *In re Marshall*, 198 U.S.P.Q. 344, 346 (C.C.P.A. 1978). Thus, in order for Gross-I to inherently anticipate the claimed invention, the method described in Gross-I must result in the claimed invention, *i.e. delivering drug into the intradermal space, thus achieving the claimed dose sparing effect, each time and every time* Gross-I' method is practiced. *Glaxo Inc. v. Novopharm Ltd.* 53 F.3d 1043 (Fed. Cir. 1995). That is, each and every time Gross-I is practiced, its method must deliver the drug into the intradermal compartment so that systemic distribution having the claimed dose sparing effect is achieved. However, as evidenced by the Gross-I patent itself in Example 1, the method disclosed in Gross-I *fails* to achieve delivery to the intradermal compartment, and therefore cannot anticipate the claimed invention.

Nothing in the remaining disclosure of Gross-I supplies the claimed features. Indeed, even Gross-I recognizes that its "intradermal device" does not specifically target the intradermal space, but rather haphazardly or non-selectively administers the drug "below the epidermis, *i.e.*, to the interface between the epidermis and the dermis or to the interior of the dermis or subcutaneously (*see* Gross-I at col. 3, *ll.* 46-52).[4] Consistently Gross-I characterizes the needles used in these devices as being of just sufficient length to penetrate through the epidermis." (Gross-I at col. 7, *ll.* 50, emphasis added.)[5] Even if Gross-I had used needles of the right length and configuration it would still not achieve intradermal delivery, as it also fails to appreciate the need for providing adequate pressures so that the substance is efficiently and consistently delivered to the intradermal compartment. In fact, Gross-I merely recognizes the need for sufficient pressure in order to pierce the stratum corneum, *i.e.*, "to stretch and pierce the epidermis" (*See* Gross-I at col. 3, *ll.* 36-37), but is silent on the need the for sufficient pressure to effectively discharge a substance so that effective delivery to the intradermal compartment occurs.

The instant specification, in contrast to Gross-I, provides the appropriate parameters to not only achieve targeted drug delivery to the intradermal space, but to do so in a controlled way (*e.g.*, controlled volume and rate) that will achieve a reduced therapeutic or diagnostic dosage. It is the Applicants' disclosure, not Gross-I, which teaches the importance

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[4] Although Gross lists intradermal delivery as an *intended* feature of the purported invention, that is a far cry from having actually delivered or targeted drug into the intradermal space. As clearly illustrated by Gross' working Example, the proposed methods and devices do not achieve intradermal targeting.

of not only the length of the needle, but the relative exposed height of the needle outlet (*e.g.*, the bevel) that could be used to successfully target the intradermal compartment. (*See*, specification at pp. 13-14, 16, 17).

Thus, in view of the foregoing, Gross-I cannot anticipate the claimed invention.

5. THE CLAIMED INVENTION IS NOT ANTICIPATED BY U.S. Patent No. 5,800,420 ("Gross-II")

Claims 1, 4, 18 and 26 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Gross *et al.*, U.S. Patent No. 5,800,420 ("Gross-II").

The Examiner contends that Gross-II discloses an intradermal drug delivery device that includes administering a substance using small gauge needles to deliver a substance into the intradermal compartment within skin. However, for reasons similar to those already discussed above, the amended claims are not anticipated by Gross-II, and the rejection should be withdrawn.

Gross-II proposes methods and devices that non-selectively administer drugs either to intradermally or subcutaneously (*see*, Gross-II at col. 5, *ll.* 26-32; and col. 6, *ll.* 30-36; col. 10, *ll.* 33-38). Gross-II does not describe delivering or targeting drugs into the intradermal compartment to achieve the systemic distribution and dose sparing effects claimed by Applicants. Thus, the claims are not anticipated by Gross-II, and the rejection should be withdrawn.

As in Gross I, Gross II does not provide the correct needle length and configuration to deliver the drug into the intradermal compartment of human skin. Gross II is devoid of any teaching relating to configuration of the needle required to prevent leakage of the drug outside the intradermal compartment. Gross II fails to provide the systemic distribution, pharmacokinetic profile or dose sparing effects of any drug. Gross II does not provide comparative dose sparing analysis with alterative routes of delivery and in effect equates its alleged ID delivery with SC delivery. Therefore, Gross-II does not anticipate the claimed invention.

6. THE CLAIMED INVENTION IS NOT ANTICIPATED BY U.S. Patent No. 6,537,242 ("Palmer")

Claims 18, 23-25, 40 and 48-50 are rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,537,242 ("Palmer"). The Examiner contends that Palmer discloses an intradermal drug delivery device that includes and array of microneedles.

The claimed invention relates to a method of delivering a substance into an intradermal compartment of a human subject's skin, said method comprising injecting or infusing the substance intradermally through one or more microneedles having a length sufficient to penetrate the intradermal compartment and an outlet at a depth within the intradermal compartment wherein the dosage of the substance for achieving a biological effect is reduced compared to when the substance is delivered to a subcutaneous compartment of the human subject's skin. The devices disclosed in Palmer are configured to deliver a substance to an "intradermal" layer which Palmer defines as "one or more layers within the skin and not limited to the dermis layer of the skin." (*see* Palmer at col. 4, *ll.* 33-35). Thus, by Palmer's own definition of intradermal layer, it does not describe delivery of a substance to the *intradermal* compartment of human skin, as described and claimed by the instant specification. As Palmer does not describe the invention as claimed, it cannot anticipate, and as such the rejection in view of Palmer should be withdrawn.

Thus, in view of the foregoing, Palmer does not anticipate the claimed invention.

7. DOUBLE PATENTING REJECTION

Claims 1-68 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-6, 12-25, 31-47, 53-56, and 62-63 of copending application 09/893,746. As this is a provisional double-patenting rejection, Applicants will not address the rejection on its merits at this time.

CONCLUSION

In light of the above amendments and remarks, the Applicant respectfully requests that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an early allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

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